## REMARKS

Claims 1-63 were pending. Claims 5 and 23 have been amended to clarify the invention. Therefore, claims 1-63 are pending. No new matter has been added.

Applicants note with appreciation that the Examiner has found claims 1-63 to be free of the prior art.

***Rejection of Claims 1-63 under 35 U.S.C. § 112, first paragraph***

Claims 1-63 were rejected under 35 U.S.C. § 112, first paragraph, because, according to the Examiner "the specification, while being enabling for non-heterocyclic substituted creatine derivatives does not reasonable provide enablement for heterocyclic substituted creatine derivatives."

Without acquiescing to the Examiner's rejection, Applicants respectfully submit that this rejection no longer pertains to the claims as amended. Therefore, Applicants respectfully request that this rejection of claims 1-63 under 35 U.S.C. § 112, first paragraph be withdrawn.

## SUMMARY

Amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's objections and/or rejections. The amendments to the claims are being made solely to expedite prosecution of the above-identified application. Applicants reserve the option to further prosecute the same or similar claims in the present or another patent application. The amendments made to the claims are not related to any issues of patentability.

In view of the remarks set forth above, it is respectfully submitted that this application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call Elizabeth A. Hanley, Esq. at (617) 227-7400.

Date: January 29, 2003

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By _____

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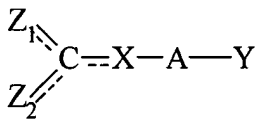
**Marked Up Version of Claims to Show Changes Made**

5. [Amended] The method of claim 1, wherein said creatine compound has the formula:



and pharmaceutically acceptable salts thereof, wherein:

a) Y is selected from the group consisting of: $-CO_2H$, -NHOH, $-NO_2$, $-SO_3H$, $-C(=O)NHSO_2J$ and $-P(=O)(OH)(OJ)$, wherein J is selected from the group consisting of: hydrogen, $C_1$-$C_6$ straight chain alkyl, $C_3$-$C_6$ branched alkyl, $C_2$-$C_6$ alkenyl, $C_3$-$C_6$ branched alkenyl, and aryl;

b) A is selected from the group consisting of: C, CH, $C_1$-$C_5$alkyl, $C_2$-$C_5$alkenyl, $C_2$-$C_5$alkynyl, and $C_1$-$C_5$ alkoyl chain, each having 0-2 substituents which are selected independently from the group consisting of:

1) K, where K is selected from the group consisting of: $C_1$ -$C_6$ straight alkyl, $C_2$-$C_6$ straight alkenyl, $C_1$-$C_6$ straight alkoyl, $C_3$-$C_6$ branched alkyl, $C_3$-$C_6$ branched alkenyl, and $C_4$-$C_6$ branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

2) an aryl group selected from the group consisting of: a 1-2 ring carbocycle ~~and a 1-2 ring heterocycle~~, wherein the aryl group contains 0-2 substituents independently selected from the group consisting of: $-CH_2L$ and $-COCH_2L$ where L is independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy; and

3) -NH-M, wherein M is selected from the group consisting of: hydrogen, $C_1$-$C_4$ alkyl, $C_2$-$C_4$ alkenyl, $C_1$-$C_4$ alkoyl, $C_3$-$C_4$ branched alkyl, $C_3$-$C_4$ branched alkenyl, and $C_4$ branched alkoyl;

c) X is selected from the group consisting of $NR_1$, $CHR_1$, $CR_1$, O and S, wherein $R_1$ is selected from the group consisting of:

1) hydrogen;

2) K where K is selected from the group consisting of: $C_1$-$C_6$ straight alkyl, $C_2$-$C_6$ straight alkenyl, $C_1$-$C_6$ straight alkoyl, $C_3$-$C_6$ branched alkyl, $C_3$-$C_6$ branched alkenyl, and $C_4$-$C_6$ branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

3) an aryl group selected from the group consisting of a 1-2 ring carbocycle ~~and a 1-2 ring heterocycle~~, wherein the aryl group contains 0-2 substituents independently selected from the group consisting of: $-CH_2L$ and $-COCH_2L$ where L is independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

4) a $C_5$-$C_9$ a-amino-w-methyl-w-adenosylcarboxylic acid attached via the w-methyl carbon;

5) a $C_5$-$C_9$ a-amino-w-aza-w-methyl-w-adenosylcarboxylic acid attached via the w-methyl carbon; and

6) a $C_5$-$C_9$ a-amino-w-thia-w-methyl-w-adenosylcarboxylic acid attached via the w-methyl carbon;

d) $Z_1$ and $Z_2$ are chosen independently from the group consisting of: =0, $-NHR_2$, $-CH_2R_2$, $-NR_2OH$; wherein $Z_1$ and $Z_2$ may not both be =0 and wherein $R_2$ is selected from the group consisting of:

1) hydrogen;

2) K, where K is selected from the group consisting of: $C_1$-$C_6$ straight alkyl; $C_2$-$C_6$ straight alkenyl, $C_1$-$C_6$ straight alkoyl, $C_3$-$C_6$ branched alkyl, $C_3$-$C_6$ branched alkenyl, and $C_4$-$C_6$ branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

3) an aryl group selected from the group consisting of a 1-2 ring carbocycle ~~and a 1-2 ring heterocycle~~, wherein the aryl group contains 0-2 substituents independently selected from the group consisting of: $-CH_2L$ and $-COCH_2L$ where L is independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

4) a $C_4$-$C_8$ a-amino-carboxylic acid attached via the w-carbon;

5) B, wherein B is selected from the group consisting of: $-CO_2H$, -NHOH, $-SO_3H$, $-N0_2$, OP(=O)(OH)(OJ) and -P(=O)(OH)(OJ), wherein J is selected from the group consisting of: hydrogen, $C_1$-$C_6$ straight alkyl, $C_3$-$C_6$ branched alkyl, $C_2$-$C_6$ alkenyl, $C_3$-$C_6$ branched alkenyl, and aryl, wherein B is optionally connected to the nitrogen via a linker selected from the group consisting of: $C_1$-$C_2$ alkyl, $C_2$ alkenyl, and $C_1$-$C_2$ alkoyl;

6) -D-E, wherein D is selected from the group consisting of: $C_1$-$C_3$ straight alkyl, $C_3$ branched alkyl, $C_2$-$C_3$ straight alkenyl, $C_3$ branched alkenyl, $C_1$-$C_3$ straight alkoyl, aryl and aroyl; and E is selected from the group consisting of: $-(P0_3)_nNMP$, where n is 0-2 and NMP is ribonucleotide monophosphate connected via the 5'-phosphate, 3'-phosphate or the aromatic ring of the base; $-[P(=O)(OCH_3)(0)]_m$-Q, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; $-[P(=O)(OH)(CH_2)]_m$-Q, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; and an aryl group containing 0-3 substituents chosen independently from the group consisting of: Cl, Br, epoxy, acetoxy, -OG, -C(=O)G, and $-CO_2G$, where G is independently selected from the group consisting of: $C_1$-$C_6$ straight alkyl, $C_2$-$C_6$ straight alkenyl, $C_1$ -$C_6$ straight alkoyl, $C_3$-$C_6$ branched alkyl, $C_3$-$C_6$ branched alkenyl, $C_4$-$C_6$ branched alkoyl, wherein E may be attached to any point to D, and if D is alkyl or alkenyl, D may be connected at either or both ends by an amide linkage; and

7) -E, wherein E is selected from the group consisting of -$(P0_3)_nNMP$, where n is 0-2 and NMP is a ribonucleotide monophosphate connected via the 5'-phosphate, 3'-phosphate or the aromatic ring of the base; $-[P(=O)(OCH_3)(0)]_m$-Q, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; $-[P(=O)(OH)(CH_2)]_m$-Q, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; and an aryl group containing 0-3

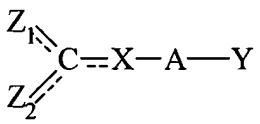
substituents chose independently from the group consisting of: $C_1$, Br, epoxy, acetoxy, -OG, -C(=O)G, and -CO=G, where G is independently selected from the group consisting of: $C_1$-$C_6$ straight alkyl, $C_2$-$C_6$ straight alkenyl, $C_1$-$C_6$ straight alkoyl, $C_3$-$C_6$ branched alkyl, $C_3$-$C_6$ branched alkenyl, $C_4$-$C_6$ branched alkoyl; and if E is aryl, E may be connected by an amide linkage;

e) if $R_1$ and at least one $R_2$ group are present, $R_1$ may be connected by a single or double bond to an $R_2$ group to form a cycle of 5 to 7 members;

f) if two $R_2$ groups are present, they may be connected by a single or a double bond to form a cycle of 4 to 7 members; and

g) if $R_1$ is present and $Z_1$ or $Z_2$ is selected from the group consisting of -$NHR_2$, -$CH_2R_2$ and -$NR_2OH$, then $R_1$ may be connected by a single or double bond to the carbon or nitrogen of either $Z_1$ or $Z_2$ to form a cycle of 4 to 7 members.

23. [Amended] The method of claim 19, wherein said creatine compound has the formula:



and pharmaceutically acceptable salts thereof, wherein:

a) Y is selected from the group consisting of: -$CO_2H$, -NHOH, -$N0_2$, - $SO_3H$, -C(=0)$NHS0_2J$ and -P(=O)(OH)(OJ), wherein J is selected from the group consisting of: hydrogen, $C_1$-$C_6$ straight chain alkyl, $C_3$-$C_6$ branched alkyl, $C_2$-$C_6$ alkenyl, $C_3$-$C_6$ branched alkenyl, and aryl;

b) A is selected from the group consisting of: C, CH, $C_1$-$C_5$alkyl, $C_2$-$C_5$alkenyl, $C_2$-$C_5$alkynyl, and $C_1$-$C_5$ alkoyl chain, each having 0-2 substituents which are selected independently from the group consisting of:

1) K, where K is selected from the group consisting of: $C_1$ –$C_6$ straight alkyl, $C_2$-$C_6$ straight alkenyl, $C_1$-$C_6$ straight alkoyl, $C_3$-$C_6$ branched alkyl, $C_3$-$C_6$ branched alkenyl, and $C_4$-$C_6$ branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

2) an aryl group selected from the group consisting of: a 1-2 ring carbocycle ~~and a 1-2 ring heterocycle~~, wherein the aryl group contains 0-2 substituents independently selected from the group consisting of: $-CH_2L$ and $-COCH_2L$ where L is independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy; and

3) -NH-M, wherein M is selected from the group consisting of: hydrogen, $C_1$-$C_4$ alkyl, $C_2$-$C_4$ alkenyl, $C_1$-$C_4$ alkoyl, $C_3$-$C_4$ branched alkyl, $C_3$-$C_4$ branched alkenyl, and $C_4$ branched alkoyl;

c) X is selected from the group consisting of $NR_1$, $CHR_1$, $CR_1$, O and S, wherein $R_1$ is selected from the group consisting of:

1) hydrogen;

2) K where K is selected from the group consisting of: $C_1$-$C_6$ straight alkyl, $C_2$-$C_6$ straight alkenyl, $C_1$-$C_6$ straight alkoyl, $C_3$-$C_6$ branched alkyl, $C_3$-$C_6$ branched alkenyl, and $C_4$-$C_6$ branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

3) an aryl group selected from the group consisting of a 1-2 ring carbocycle ~~and a 1-2 ring heterocycle~~, wherein the aryl group contains 0-2 substituents independently selected from the group consisting of: $-CH_2L$ and $-COCH_2L$ where L is independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

4) a $C_5$-$C_9$ a-amino-w-methyl-w-adenosylcarboxylic acid attached via the w-methyl carbon;

5) a $C_5$-$C_9$ a-amino-w-aza-w-methyl-w-adenosylcarboxylic acid attached via the w-methyl carbon; and

6) a $C_5$-$C_9$ a-amino-w-thia-w-methyl-w-adenosylcarboxylic acid attached via the w-methyl carbon;

d) $Z_1$ and $Z_2$ are chosen independently from the group consisting of: =0, $-NHR_2$, $-CH_2R_2$, $-NR_2OH$; wherein $Z_1$ and $Z_2$ may not both be =0 and wherein $R_2$ is selected from the group consisting of:

1) hydrogen;

2) K, where K is selected from the group consisting of: $C_1$-$C_6$ straight alkyl; $C_2$-$C_6$ straight alkenyl, $C_1$-$C_6$ straight alkoyl, $C_3$-$C_6$ branched alkyl, $C_3$-$C_6$ branched alkenyl, and $C_4$-$C_6$ branched alkoyl, K having 0-2 substituents independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

3) an aryl group selected from the group consisting of a 1-2 ring carbocycle ~~and a 1-2 ring heterocycle~~, wherein the aryl group contains 0-2 substituents independently selected from the group consisting of: $-CH_2L$ and $-COCH_2L$ where L is independently selected from the group consisting of: bromo, chloro, epoxy and acetoxy;

4) a $C_4$-$C_8$ a-amino-carboxylic acid attached via the w-carbon;

5) B, wherein B is selected from the group consisting of: $-CO_2H$, -NHOH, $-SO_3H$, $-N0_2$, OP(=O)(OH)(OJ) and -P(=O)(OH)(OJ), wherein J is selected from the group consisting of: hydrogen, $C_1$-$C_6$ straight alkyl, $C_3$-$C_6$ branched alkyl, $C_2$-$C_6$ alkenyl, $C_3$-$C_6$ branched alkenyl, and aryl, wherein B is optionally connected to the nitrogen via a linker selected from the group consisting of: $C_1$-$C_2$ alkyl, $C_2$ alkenyl, and $C_1$-$C_2$ alkoyl;

6) -D-E, wherein D is selected from the group consisting of: $C_1$-$C_3$ straight alkyl, $C_3$ branched alkyl, $C_2$-$C_3$ straight alkenyl, $C_3$ branched alkenyl, $C_1$-$C_3$ straight alkoyl, aryl and aroyl; and E is selected from the group consisting of: $-(P0_3)_nNMP$, where n is 0-2 and NMP is ribonucleotide monophosphate connected via the 5'-phosphate, 3'-phosphate or the aromatic ring of the base; $-[P(=O)(OCH_3)(0)]_m$-Q, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of

the base; -[P(=O)(OH)($CH_2$)]$_m$-Q, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; and an aryl group containing 0-3 substituents chosen independently from the group consisting of: Cl, Br, epoxy, acetoxy, -OG, -C(=O)G, and -$CO_2$G, where G is independently selected from the group consisting of: $C_1$-$C_6$ straight alkyl, $C_2$-$C_6$ straight alkenyl, $C_1$ -$C_6$ straight alkoyl, $C_3$-$C_6$ branched alkyl, $C_3$-$C_6$ branched alkenyl, $C_4$-$C_6$ branched alkoyl, wherein E may be attached to any point to D, and if D is alkyl or alkenyl, D may be connected at either or both ends by an amide linkage; and

7) -E, wherein E is selected from the group consisting of -($P0_3$)$_n$NMP, where n is 0-2 and NMP is a ribonucleotide monophosphate connected via the 5'-phosphate, 3'-phosphate or the aromatic ring of the base; -[P(=O)($OCH_3$)(0)]$_m$-Q, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; -[P(=O)(OH)($CH_2$)]$_m$-Q, where m is 0-3 and Q is a ribonucleoside connected via the ribose or the aromatic ring of the base; and an aryl group containing 0-3 substituents chose independently from the group consisting of: $C_1$, Br, epoxy, acetoxy, -OG, -C(=O)G, and -CO=G, where G is independently selected from the group consisting of: $C_1$-$C_6$ straight alkyl, $C_2$-$C_6$ straight alkenyl, $C_1$-$C_6$ straight alkoyl, $C_3$-$C_6$ branched alkyl, $C_3$-$C_6$ branched alkenyl, $C_4$-$C_6$ branched alkoyl; and if E is aryl, E may be connected by an amide linkage;

e) if $R_1$ and at least one $R_2$ group are present, $R_1$ may be connected by a single or double bond to an $R_2$ group to form a cycle of 5 to 7 members;

f) if two $R_2$ groups are present, they may be connected by a single or a double bond to form a cycle of 4 to 7 members; and

g) if $R_1$ is present and $Z_1$ or $Z_2$ is selected from the group consisting of -$NHR_2$, -$CH_2R_2$ and -$NR_2$OH, then $R_1$ may be connected by a single or double bond to the carbon or nitrogen of either $Z_1$ or $Z_2$ to form a cycle of 4 to 7 members.